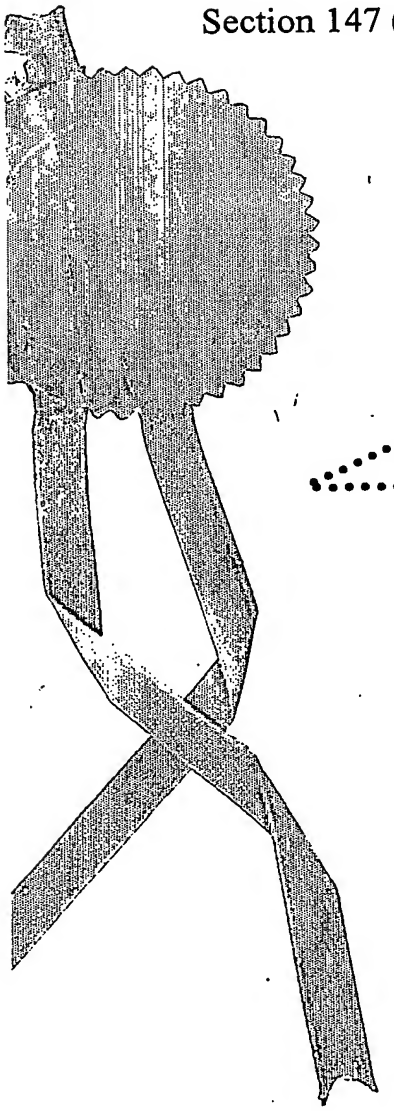
THE PATENT ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Complete specification filed on 17/6/2002 in respect of Patent Application No. 533/MUM/2002 of Themis Laboratories Private Limited, Unit No.S-4 Khira Industrial Estate, B.M. Bhargava Road, Santacruz (w), Mumbai 400 054, Maharashtra State, India...

This certificate is issued under the powers vested on me under Section 147 (1) of the Patents Act, 1970.



Dated this 22nd day of November 2002.

(N. K. GARG)
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FORM 1

THE PATENT ACT, 1970

(39 of 1970)

Application for Grant of a PAtent

(See Sections 5(2), 7, 54 and 135 and Rule 33 A)

1. We,

(a) Themis Laboratories Private Limited

(b) Unit No. S-4, Khira Industrial Estate, B. M. Bhargava Road, Santacruz (West), Mumbai – 400 054, Maharashtra State, India

(c) an Indian Company incorporated under the Companies Act, 1956

2. Hereby declare : -

(a) that we are in possession of an invention titled :

" Process Of Manufacture of Novel Drug Delivery System : Multilayer Tablet Composition of Thiazolidinedione and Biguanides ".

(b) that the Complete Specification relating to this invention is filed with this Application.

(c) that there is no lawful ground of objection to the grant of a Patent to us.

ORIGINAL

3. Further declare that the inventors for the said invention are

(1) Mr. Antarkar Amit Krishna, House No. C / 4 , Rani Laxmi Nagar, Nagpur – 440 022, State of Maharashtra, India, Indian

(2) Dr. Lala Rajendra Ghanshamlal, House No. 100, " Guru Cottage ", Inlaks Hospital Road, Chembur, Mumbai – 400 074, State of Maharashtra, India, Indian

(3) Mr. Kamdar Nirav Mahendra, Dina Patil Estate, Block No. B – 6, 1st Floor, Station Road, Bhandup (West), Mumbai 400 078, State of Maharashtra, India, Indian

(4) Dr. Gadkari Parag Narayan, 23 / 703 Anant, Vasant Vihar, Pokhran Road 2, Thane (-West) – 400 607, State of Maharashtra, India. Indian

(5) Mrs. Shah Maya Janak, 30, " Saujanya ", 3rd N. S Road, Vallabhnagar Society, Vile Parle (West), Mumbai – 400 056, State of Maharashtra, India, Indian

(6) Mr. Shah Janak Ramanlal, 30, " Saujanya ", 3rd N. S Road, Vallabhnagar Society, Vile Parle (West), Mumbai – 400 056, State of Maharashtra, India, Indian

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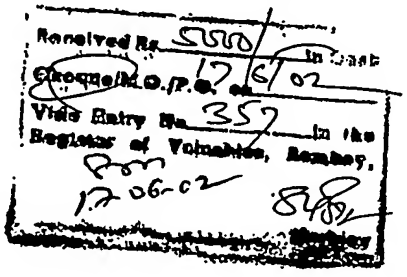


4. That we are the Assignees of the true and first inventors.

5. That our address for service in India is as follows : -

M/s. Bharat Shah & Co.,
Advocates & Solicitors,
1, Gr. Floor, God's Gift,
St. Francis Road,
Vile Parle (West),
Mumbai – 400 056.

6. Following declaration was given by the inventors declare that the applicants herein are our Assignees.

Amit Antarkar
(Antarkar Amit Krishna)

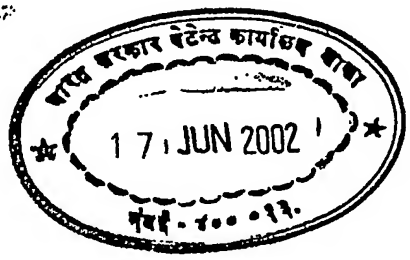
(Lala Rajendra Ghanshamlal)

Nirav M. Kamdar.
(Kamdar Nirav Mahendra)

(Gadkari Parag Narayan)

MShah
(Mrs. Shah Maya Janak)

(Mr. Shah Janak Ramanlal)



7. That to the best of our knowledge, information and belief the fact and matters stated therein are correct and that there is no lawful ground of objection to the grant of Patent to us on this application.

8. Following are the attachment with the application : -

(a) Complete Specification (3 Copies)

(b) Power of Authority.

(c) Fees Rs. 5,000/- in cheque bearing No. 883088 date 12-6-02 on Bank of Maharashtra. Bank.

We request that a Patent may be granted to us for the said invention.

Dated this 15th day of June, 2002.

For Themis Laboratories Private Limited

( )

Director / Company Secretary

To,

The Controller of Patents,

Patents office, Mumbai.

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

COMPLETE SPECIFICATION

"A Process Of Manufacture of Novel Drug Delivery System : Multilayer Tablet Composition of Thiazolidinedione and Biguanides"

Themis Laboratories Pvt. Ltd, Mumbai, a company incorporated under the companies act, 1956 and having its corporate office at Unit No. S-4, Khira Industrial Estate, B M Bhargava Road, Santacruz(W) Mumbai 400 054. Maharashtra State. INDIA

The following specification particularly describes and ascertain the nature of this invention and the manner in which it is to be performed.

A Process Of Manufacture of Novel Drug Delivery System : Multilayer Tablet Composition of Thiazolidinedione and Biguanides

Abstract :

A process for manufacture of novel drug delivery multilayer tablet composition for instant release of Thiazolidinediones and prolonged release of Biguanides which comprises of minimum of two layers wherein one outer layer may comprise of a mixture of excipients & Thiazolidinedione allowing immediate release of Thiazolidinedione and the other layer arranged in contact with the immediate release layer which comprises of biguanide, mixture of excipients and a minimum of one or more prolonged release polymer in which the biguanide is embedded allowing for prolonged release of the biguanide up to a period of 10 hours.

The prolonged release core tablets of biguanide may be film coated from the suspension containing Thiazolidinedione and excipients for immediate release of Thiazolidinedione and/or for aesthetic appeal.

The bilayer tablets may be enrobed into soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile.

Background of Invention:

Diabetes mellitus is a major health care problem not only in the developing countries but also in the developed countries. Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by disorders in lipid

metabolism glycometabolism, obesity as well as circulatory disorders. The disease is progressive in nature and needs attention as it leads to complications in many cases. Although in the initial stages the disease can be controlled by diet itself, but generally requires treatment with drugs. The main therapeutic goal in type 2 Diabetes Mellitus (DM) ie non- insulin dependent Diabetes Mellitus is to control hyperglycemia & prevent hypoglycemia due to derangements of insulin resistance & impaired insulin secretion. Therefore, it is necessary to select the drug for the prevailing Disease State in each individual case so as to have a better glycemic control. However, this selection of drug is often difficult in clinical settings because single use of each individual drug can not bring sufficient glycemic control and there are various other problems such as side effect, which is caused by an increased dose or a long-term administration.

It has now been discovered that combination therapy often results in dramatic improvement in glycemic control, and that even better control can be achieved by using a large dose of single active ingredients. A combination of antihyperglycemia agents are required to have an additive / synergistic therapeutic effect which can restore glucose control when one single agent alone is not successful. Accordingly, such combinations are especially useful in treating diabetes and associated complications.

This invention relates to the process of manufacturing multilayer tablet comprising of combination of anti-hyperglycemic drugs in which the release of one anti- hyperglycemic drug is instant and other anti- hyperglycemic drug is prolonged.

Thiazolidinediones, a new class of compound are insulin sensitivity enhancers also known as insulin resistance deblockers are gaining much attention as they have the action to normalize the impaired insulin receptor function. They increase insulin receptor expression in adipocytes & hepatocytes. They also facilitates expression of GLUT 1 & GLUT 4 which plays a key role in facilitating glucose transport into adipocytes & skeletal muscle by 10 & 7 folds respectively. In skeletal muscles they facilitate glucose uptake & also stimulate glycogen synthesis. Since these actions of these anti-hyperglycemic drugs are comparatively gradual and the risk of side effect in long-term administration is also low, these compound are useful for obese patients who are presumed to be highly insulin-resistant.

Biguanides, an another class of anti- hyperglycemic drug can reduce blood glucose level even in the absence of functioning pancreatic beta cells & circulating insulin. Exact mode of action is not known but proposed mechanisms are :

a) Reduction of new glucose synthesis in liver.

b) Reduction of plasma glucose level.

c) Reduction of glucose absorption from intestine.

d) Stimulation of glycolysis in tissue with resultant removal of glucose from blood & improvement of insulin resistance. But biguanides are short acting & require frequent administration.

Biguanides have to be delivered in large doses, sometimes several times a day to achieve desired therapeutic activity. Multiple dosing regimens together along

with large doses are not preferred because of patient non-compliance, potential side effects & danger of overdosing. So it becomes imperative to shift / transit multiple dosing to once-a-day or twice-a-day dosing regimens, especially when large doses of drug have to be delivered over a prolonged period.

Since biguanides can act even in non-functioning pancreatic beta cells or circulating insulin, the combination of biguanide with thiazolidinediones forms a logical choice as they have different mode of action. As biguanides has short half-life, providing it in prolonged release form will not only reduce the frequency of administration but also dose related side effect. Hence, providing a combination thiazolidinediones type of anti-hyperglycemic drug with biguanides in which biguanide is in prolonged release is a step forward in improving anti-diabetic drug management. A combined form of the drugs, i.e. a single integral unit in which the biguanide is in prolonged release thereof has not been reported. The present invention provides such a single integral unit in which biguanide is in prolonged release form.

The production of the two-layer tablet containing two different drugs is an extremely popular method for improving sales appeal. However, in the conventional method comprising of 2 drug, both the drugs are granulated as single granules and the said granules are divided in two lots. These granules are lubricated and compressed on a tablet machine having two layer compression facilities.

The main disadvantage of this conventional method is that either both the drugs are released immediately which may lead to hypoglycemia or any other adverse

effect or release of both the drugs will be prolonged if any prolonged release polymer is present. In this case instant bioavailability of the drug will not be seen and therapeutic effect of the drug will be delayed which may be fatal in case of emergency. So by administering the formulation of the invention which is made by the novel process it is possible to have instant release of one drug and prolonged release of other drugs for better management of the disease.

Secondly, biguanide such as Metformin HCl is a cohesive white powder and has a hygroscopicity measured at 95% relative humidity at 25°C of greater than 20% moisture uptake at 6 hours and has a property of forming hard lumps under its own weight. Further Metformin HCl has a poor compressibility. Therefore, handling of Metformin HCl in a pharmaceutical manufacturing facility could present problems especially in high humidity environments. But the granules prepared by the process of the invention can be stored and show minimal increase in the moisture content and no lump formation is observed. The core tablet of Metformin HCl, which is prepared by the process of the invention have a good compressibility, no capping and a hardness of not less than 5kg/cm^2 and a friability of less than 1%. The formulation is stable atleast for a period of 2 years.

Summary of the invention:

This invention comprises of a process of novel drug delivery multilayer tablet composition for the instant release of Thiazolidinedione such as Pioglitazone HCl and & prolonged release of biguanide such as Metformin HCl, so as to maintain blood level for 24 hours after once a day administration. The formulation

comprises of minimum two superimposed layers, characterized in that; the first layer is composed of Metformin HCl granules containing Metformin HCl, a minimum of one or more polymer & a mixture of excipients in which Metformin HCl is embedded in the polymer matrix. This polymeric matrix will allow for prolonged release of Metformin HCl up to a period of 10-hrs in-vitro.

A second layer, which is in contact with the said first layer, comprises of Pioglitazone HCl and a mixture of excipients allowing immediate release of Pioglitazone HCl.

The said granules of Metformin HCl and Pioglitazone HCl are loaded in two hopper of a tablet compression machine and then compressed into capsule shaped, biconvex, bilayered tablets having a prolonged release of Biguanide upto a period of 10 hours.

Granules for the first layer, which is composed of Metformin HCl, polymer & a mixture of excipients in which Metformin HCl is embedded in the polymer matrix is compressed into core tablet of Metformin HCl. This core tablet is then film coated from suspension containing Pioglitazone HCl and a mixture of excipients for immediate release of Pioglitazone HCl and/or for enhancing the appearance.

The bilayered tablets may be enrobed into soft gelatin ribbons for ease of swallowing, additional protection against oxidation, photodegradation, identification, taste masking, and or for aesthetic appeal without altering the dissolution profile.

Description:

This invention relates a process of novel drug delivery multilayer tablet composition for the instant release of Thiazolidinedione such as Pioglitazone HCl and & prolonged release of Biguanide such as Metformin HCl. Instant release of Pioglitazone HCl from the formulation will ensure its instant bioavailability, which is desirable for better hyperglycemic control. In case of Metformin HCl, which has short half-life, therapeutic activity is confined only for short period of time. Bioavailability of Metformin HCl is also hampered. So for improvisation of bioavailability of Metformin HCl and for effective drug therapy it becomes imperative for continuous & regular supply of Metformin HCl.

However in prior art, the kinetics of release of Pioglitazone HCl and Metformin HCl depends on many factors like enzyme system, pH condition, physiological state of individual which varies from one individual to another (inter subject variation) & on the fasting or fed condition of the individual, physical state of mind, emotional status (intra subject variation).

Further, pH condition varies all along the GI tract. Thus it becomes difficult to predict in-vivo level of Metformin HCl and Pioglitazone HCl after administration of instant release system.

The objective of the present investigation / invention is to overcome this issue by administering the formulation which will hold its integrity for release characteristic of Metformin HCl and Pioglitazone HCl irrespective of the conditions of administration in-vivo and its process of its manufacture.

Bilayered tablets of the invention produce pH independent release of the Metformin HCl in-vitro. By making use of the tablet of this invention it is possible to optimize & regulate the supply of Metformin HCl in the body considering the factor of subject tolerance to active pharmacokinetic & pharmacodynamic factor.

More precisely the invention relates to the process of formulation of bilayer tablet for instant & prolonged released of Pioglitazone HCl and Metformin HCl comprising minimum two superimposed layers characterized in that.

First layer is composed of Metformin HCl granules containing Metformin HCl, polymer & a mixture of excipients in which Metformin HCl is embedded in the polymer matrix. This polymeric matrix will allow for prolonged release of Metformin HCl up to a period of 10-hrs in-vitro. The second layer, which is arranged in contact with first layer, comprises of Pioglitazone HCl and a mixture of excipients allowing immediate release of Pioglitazone HCl is either completely covered / enveloped/ enclosed by the first layer or only partially covered by it. In second case, only one surface of second layer is in contact with the first layer i.e. two layers have one outer surface each & the other surface is in contact with one another. In this type of tablet the shape is unimportant and is of capsule shaped & tablet is designated as " Containing Parallel Layers ".

The tablet of the invention, which is preferably bilayered however also, encompasses multilayer tablet as long as they comprise of combination of two layers as defined above.

The important characteristic of the invention is that from the same single integral unit, Metformin HCl from first layer is released over a period of 10 hours while the

second layer containing Pioglitazone HCl disintegrates quickly and releases Pioglitazone HCl rapidly at the site of administration.

The first layer from which the release of Metformin HCl is prolonged comprises of minimum of one or more hydrophilic, inert, non-biodegradable plastic / porous polymer matrix, which swells & erodes in aqueous media & subsequently, releases the drug in the surrounding environment. The rate and the degree of swelling of the polymer depend on the molecular weight and viscosity range of the polymers. The polymer is selected but not limited to Hydroxypropylmethylcellulose alone or combination of Hydroxypropylmethylcellulose with Sodium Carboxymethylcellulose or combination of Hydroxypropylmethylcellulose with Hydroxypropylcellulose or combination of Hydroxypropylmethylcellulose with Hydroxyethylcellulose or combination of Hydroxypropylmethylcellulose with Sodium Alginate or combination of Hydroxypropylmethylcellulose with Xanthan Gum or combination of Hydroxypropylmethylcellulose with Guar gum or combination of Hydroxypropylmethylcellulose with Sodium Carboxymethylcellulose and Meth(acrylic) acid Copolymers or combination of Hydroxypropylmethylcellulose with Sodium Alginate and Meth(acrylic) acid copolymer.

The copolymers derived from (meth)acrylic acids comprise the copolymers of derivatives of methacrylic acid and the copolymers of derivatives of acrylic acid and of derivatives of methacrylic acid. According to a preferred embodiment of the invention, the non-biodegradable inert polymeric material is chosen from the groups consisting of ethyl acrylate and methyl methacrylate copolymers,

ethylammonium methacrylate and methyl acrylate copolymers, ethylammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethylammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers.

Among these polymers the copolymer of methacrylic acid and ethyl acrylate is preferred. The molecular weight of these polymers varies to a very large extent depending on the nature of the monomer constituting the polymer and is generally more than or equal to 100,000.

Since the above mentioned single or combination of polymeric matrix is prolonging the release of Metformin HCl, they are generally of medium to high viscosity range, the specification of which is stated below. Hydroxypropylmethylcellulose has a nominal viscosity of a 2%w/w aqueous solution at 20°C of not less than 3000cP. Hydroxypropylcellulose has a nominal viscosity of 1% aqueous solution at 25°C of not less than 1500cP. Hydroxyethylcellulose has a nominal viscosity of 1% aqueous solution at 25°C of not less than 1500cP. Sodium Carboxymethylcellulose has a nominal viscosity of a 1%w/w aqueous solution at 25°C of not less than 1500 cP. Sodium alginate has a nominal viscosity of a 1%w/w aqueous solution at 20°C of not less than 50cP. Xanthan gum has a nominal viscosity of a 1%w/v aqueous solution at 25°C of not less than 1200 cP and Guar gum has a nominal viscosity of a 1%w/v aqueous dispersion of not less than 2000 cP.

The quantity of the single polymer or combination of the polymers used is preferably between 35 - 75 % by weight of the Metformin HCl and in case of combination of polymers, the polymers are used in the ratio of 1 : 0.01 - 1 : 3.5 or 1 : 0.01: 0.1 - 1: 3.5 : 0.3 as the case may be.

For bilayered tablets there are minimum of two possibilities.

1) In the first case of the bilayered tablets where both the layers are parallel to each other i.e. the second layer has upper surface & lower surface only one of those surface being in contact with the first layer.
2) In the second case of the bilayered tablets both the layers.are concentric to each other.

The process for the manufacture of novel drug delivery bilayer tablet composition which is the subject of the invention, where both the surface are parallel to each other is as follows.

Preparation of granules for the first Layer

1) Blending of Metformin HCl with polymer/s selected from above is carried out in planetary mixer, octagonal blender, double cone blender, rotary mixer granulator, drum mixer, ribbon blender fluid bed processor or any other suitable mixer.
2) The resultant mixture is granulated using suitable granulating solvents such as water and/or Isopropyl alcohol and/or (Meth)acrylic acid copolymer with plasticizer and binders. Whenever Isopropyl alcohol is used in combination with water it can be used in any proportion. Moreover binders is also

incorporated in the granulating solvents. Among the various classes available for the selection of binders, the binder is selected from but not limited to Hydroxypropylmethylcellulose, Polyvinylpyrrolidone, Hydroxypropylcellulose. Granulation is carried out using this binder solution in a suitable mixer granulator or fluid bed granulator. During the granulation step the polymer will hydrate and swells and Metformin HCl will be embedded in the polymeric matrix. If meth(acrylic) acid copolymer is used as the granulating agent, plasticizer is dissolved in the above mentioned granulating solvents and added to the meth(acrylic) acid copolymer and is used for granulation, followed by the granulating solvents.

3) The granules, which are obtained in the 2nd step, are then dried by the conventional method using tray drier or fluid bed drier.

4) The granules are dried to desired moisture content (NMT 4%) and the dried granules are then sized to desired size (1.7mm or less) using multimill, Fitz mill, oscillating mill or any other suitable mill.

5) The milled granules are then lubricated. The lubricating agents or glidants or antiadherants are selected but not limited to talc, Colloidal silicon dioxide, stearic acid, magnesium stearates, and calcium stearates. The lubrication is carried out in planetary mixer, octagonal blender, double cone blender, rotay mixer granulator, drum mixer, ribbon blender fluid bed processor or any other suitable mixer.

The resultant lubricated granules of Metformin HCl are ready for compression to form a first layer.

Preparation of granules for the second Layer

Blending of Pioglitazone HCl (100 microns or less) with fillers, wetting agents, disintegrants, binders, lubricants and permitted colours are carried out in planetary mixer, octagonal blender, double cone blender, rotary mixer granulator, drum mixer, ribbon blender fluid bed processor or any other suitable mixer.

Among the fillers there may be chosen any one or the combination thereof Microcrystalline Cellulose, Lactose, Dibasic Calcium Phosphate.

Wetting agents are selected but not limited to tween 80 and/or sodium lauryl sulfate. These agents aid in wetting and hence dissolution of Pioglitazone HCl in physiological environment.

The most important characteristic of the second layer is that it disintegrates instantaneously and releases Pioglitazone HCl when it comes in contact with water or physiological fluids. Among the various disintegrants, which are available, the disintegrants are selected but not limited to Sodium Starch Glycolate, Crosscarmellose Sodium, crosspovidone, starch, pregelatinised starch.

Among the binders, which is selected but not limited to Hydroxypropylmethylcellulose, Polyvinylpyrrolidone, Hydroxypropylcellulose.

The lubricating agents or glidants or antiadherants are selected but not limited to talc, Colloidal silicon dioxide, stearic acid, magnesium stearates, and calcium stearates.

The resultant lubricated granules of Pioglitazone HCl are ready for compression to form a second layer.

However, the invention is not limited to carrying out a wet granulation method for the first layer and direct compression for the second layer. Thus, persons skilled in the art will also be able to use the other existing granulation methods, such as the dry granulation method and direct compression method for the first layer and wet granulation method for the second layer.

The said granules of Biguanide and Thiazolidinedione are loaded in two different hopper of a tablet compression machine and then compressed into capsule shaped, biconvex, bilayered tablets having a instant release of Pioglitazone HCl and prolonged release of Metformin HCl upto a period of 10 hours.

The process for the manufacture of novel drug delivery bilayer tablet composition which is the subject of the invention, where both the layers are concentric to each other are as follows.

Preparation of Metformin HCl core tablet as first Layer

The lubricated granules of Metformin HCl are prepared as described in first case. The said granules are loaded in hopper of a tablet compression machine and then compressed as first layer into capsule shaped, biconvex prolonged release core containing Metformin HCl.

Loading of Pioglitazone HCl as second Layer on core tablets

Pioglitazone HCl is suspended and / or dissolved in suitable solvents along with film coating agents, wetting agents plasticizers, glidants and permitted colorants. The resultant suspension containing Thiazolidinedione is then deposited as

second layer on the prolonged release core containing Metformin HCl in fluid bed processor or coating pan.

The solvents in which Pioglitazone HCl is suspended or dissolved is selected but not limited to methanol, ethanol, dimethylformamide, dimethylsulfoxide, water, methylene chloride.

Film coating agents is selected but not limited to Hydroxypropylmethylcellulose, Polyvinylpyrrolidone and Hydroxypropylcellulose.

Wetting agents are selected but not limited to tween 80 and/or sodium lauryl sulfate. These wetting agents aid in wetting and dissolution of Pioglitazone HCl both in solvents and in physiological environment.

Plasticizer, which is incorporated, imparts flexibility and strength to the film of the film coating agents is selected but not limited to tween 80 and/or triacetin and/or polyethylene Glycol and it comprises of 5-25%by weight of the said polymer.

Glidants which are added to the solution or suspension prevents sticking of the core tablets to each other during the process are selected but not limited to talc, Colloidal silicon dioxide, stearic acid, magnesium stearates, calcium stearates and Glycerine monostearate.

The first layer comprises of 50-80% by weight of Metformin HCl and second layer comprises of 5-50% by weight of Pioglitazone HCl.

The respective proportions of first layer and the second layer whatever the case may be are not critical according to the invention.

Bilayer tablets which are prepared, whatever the case may be, gives a pH independent in-vitro dissolution release profile for Metformin HCl using USP

Dissolution Apparatus II (Dissolution Media - Distilled Water or 0.1N HCl or pH 6.8 Phosphate Buffer, Media Volume 900ml).

Time Interval (Hours)	Range of % Drug Released
1	20-50
4	50-80
8	NLT 75%

The bilayered tablet which is formulated may be further enrobed into soft gelatin ribbons for ease of swallowing & / or for additional protection against photodegradation & oxidation & / or for taste masking and / or identification and / or for aesthetic appeal without altering the dissolution profile.

The bilayer tablet of the invention is used for controlling non-insulin dependent diabetes mellitus. The active substance is selected from the group of Biguanide and Thiazolidinedione. Metformin HCl and Pioglitazone HCl are selected as the drug for the first layer and the second layer. But this invention is not restricted to these drugs but also other drugs of the same class.

Examples of the drug in the class of Biguanides include Phenformin, Buformin and Metformin and their Pharmaceutically acceptable salts.

Examples of the drug in the class of Thiazolidinediones include Rosiglitazone, Troglitazone and Pioglitazone and their pharmaceutically acceptable salts.

The dose of Metformin HCl per tablet is in the range of 250mg -2000mg and the dose of Pioglitazone HCl equivalent to Pioglitazone per tablet is in the range of 15 - 60 mg and dosage regime is 1-4 tablets once a day.

The examples provided in the text which follows illustrate the invention more clearly.

Example 1

Preparation of the tablets containing parallel layers

Preparation of granules for the first Layer

The constituents for the preparation of the first layer (prolonged layer) in the text, which follows, was used in the following proportions by weight.

Metformin HCl	62.5%
Hydroxypropylmethylcellulose	36%
Polyvinylpyrrolidone k30	0.5%
Talc	0.25%
Colloidal Silicon Dioxide	0.5%
Magnesium stearate	0.25%
Total	100%

Metformin HCl and Hydroxypropylmethylcellulose are introduced in a mixer granulator and mixing was carried out for 10 minutes. Polyvinylpyrrolidone k30 is dissolved in granulating solvent (Isopropyl alcohol and water in the ratio of 80:20). This solution is then added to the resultant mixture into the mixer granulator and large size granules are obtained. The granules are then dried in hot air oven or fluid bed drier to moisture content of not more than 4%.

The dried granules are the sized using multimill to a desired size (1.7mm or less) and the sized granules are lubricated with Talc, Colloidal Silicon Dioxide and

Magnesium stearate and the resultant lubricated granules of Metformin HCl are ready for compression to form a first layer.

Preparation of granules for the second Layer

The constituents for the preparation of the second layer (instant release layer) in the text, which follows, was used in the following proportions by weight.

Pioglitazone HCl	10%
Microcrystalline Cellulose	69%
Sodium Starch Glycolate	10%
Polyvinylpyrrolidone k30	3.84%
Sodium lauryl sulfate	0.5
Talc	1.21%
Colloidal Silicon Dioxide	3.03%
Magnesium stearate	1.21%
Lake of Sunset Yellow	1.21%
Total	100%

Pioglitazone HCl (100#) is sandwiched between Microcrystalline cellulose, Sodium Starch Glycolate and Polyvinylpyrrolidone k30 in a mixer granulator. Mixing is carried out for 10 minutes. Lake of Sunset Yellow, Colloidal Silicon Dioxide, talc and Magnesium stearate is then introduced in the mixer and mixing is carried for 10 minutes. The resultant lubricated granules of Pioglitazone HCl are ready for compression to form a second layer.

The said granules of Metformin HCl and Pioglitazone HCl are loaded in two different hopper of a tablet compression machine and then compressed into capsule shaped, biconvex, bilayered tablets.

Example 2

The other examples of the formulation of the granules for the prolonged release of Metformin HCl are

Metformin HCl	69%
Hydroxypropylmethylcellulose	25.8%
Guar Gum	2.8%
Polyvinylpyrrolidone k30	1%
Talc	0.35%
Colloidal Silicon Dioxide	0.7%
Magnesium stearate	0.35%
Total	100%

Granulation is carried out as described in example 1. Alternatively granulation can also be carried out in fluid bed processor where the mixture of Metformin HCl, Hydroxypropylmethylcellulose and Guar Gum is loaded in the fluid bed processor and the granulating solvent containing the binder Polyvinylpyrrolidone k30 is sprayed. Then the granules are dried in fluid bed processor and lubricated as described in example 1.

Example 3

Metformin HCl	59.5%
Hydroxypropylmethylcellulose	9%
Sodium Carboxymethylcellulose	27%
Copolymer of methacrylic acid and ethyl acrylate	2.4%
Polyethylene Glycol 6000	0.24%
Polyvinylpyrrolidone k30	0.86%
Talc	0.25%
Colloidal Silicon Dioxide	0.5%
Magnesium stearate	0.25%
Total	100%

Bilayered tablets can be prepared on the similar lines as described in example 1 using these formulae.

Claims

We claim

1. A process for manufacture of novel drug delivery multilayer tablet composition for instant release of Thiazolidinediones and prolonged release of Biguanides for once a day administration which comprises of minimum of two layers wherein, the tablet can be produced by ,

   Blending of Biguanide with polymers for prolonged release in suitable mixer, the resultant mixture is granulated using suitable granulating solvents such as water and/or Isopropyl alcohol and/or (Meth)acrylic acid copolymer with plasticizers and binders, thereafter the granules are dried in a suitable drier, the dried granules are then sized to desired size (1.7mm or less) and the sized granules are lubricated and the resultant lubricated granules of Biguanide are ready for compression to form a first layer, or

   The said granules of biguanide are loaded in hopper of a tablet compression machine and then compressed as first layer into capsule shaped, biconvex prolonged release core containing biguanide.

   Blending of Thiazolidinedione with fillers, disintegrants, binders, wetting agents, lubricants and permitted colours are carried out in suitable mixer and the resultant lubricated granules of Thiazolidinedione are ready for compression to form a second layer;

   The said granules of Biguanide and Thiazolidinedione are loaded in two hoppers of a tablet compression machine and then compressed into capsule

shaped, biconvex, bilayered tablets having a prolonged release of Biguanide upto a period of 10 hours having hardness of not less than 5kg/cm^2, or Thiazolidinedione is suspended and / or dissolved in suitable solvents along with film coating agents, plasticizers, wetting agents, glidants and permitted colorants. The resultant suspension containing Thiazolidinedione is then deposited as second layer on the prolonged release core containing Biguanide in fluid bed processor or coating pan.

2. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein the polymer for prolonging the release of Biguanide is Hydroxypropylmethylcellulose alone or combination of Hydroxypropylmethylcellulose with Sodium Carboxymethylcellulose or combination of Hydroxypropylmethylcellulose with Hydroxypropylcellulose or combination of Hydroxypropylmethylcellulose with Hydroxyethylcellulose or combination of Hydroxypropylmethylcellulose with Sodium Alginate or combination of Hydroxypropylmethylcellulose with Xanthan Gum or combination of Hydroxypropylmethylcellulose with Guar gum or combination of Hydroxypropylmethylcellulose with Sodium Carboxymethylcellulose and (Meth)acrylic acid Copolymers or combination of Hydroxypropylmethylcellulose with Sodium Alginate and (Meth)acrylic acid copolymer.

3. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 and 2 wherein the polymer or combination of the polymers comprises of 35 - 75 % by weight of the biguanide.

4. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim1,2 and 3 wherein the polymers are used in the ratio of 1 : 0.01 - 1 : 3.5 or 1 : 0.01: 0.1 - 1: 3.5 : 0.3 as the case may be.
5. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim1,2,3 and 4 wherein, biguanide has a pH independent in-vitro dissolution release profile using USP Dissolution Apparatus II (Dissolution Media - Distilled Water or 0.1N HCl or pH 6.8 Phosphate Buffer, Media Volume 900ml)

20-50%	1st hour
50-80%	4th hour
NLT 75%	8th hour

6. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim1and 2 where in,

HydroxyPropylMethylCellulose has a nominal viscosity of a 2%w/w aqueous solution at 20°C of not less than 3000cP. HydroxyPropylCellulose has a nominal viscosity of 1% aqueous solution at 25°C of not less than 1500cP. HydroxyEthylCellulose has a nominal viscosity of 1% aqueous solution at 25°C of not less than 1500cP. Sodium CarboxyMethylCellulose has a nominal viscosity of a 1%w/w aqueous solution at 25°C of not less than 1500 cP. Sodium alginate has a nominal viscosity of a 1%w/w aqueous solution at 20°C of not less than 50cP. Xanthan gum has a nominal viscosity of a 1%w/v aqueous solution at 25°C of not less than 1200 cP and Guar gum

has a nominal viscosity of a 1%w/v aqueous dispersion of not less than 2000 cP.

7. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the fillers are selected but not limited to Microcrystalline Cellulose and/or Lactose and/or Dibasic Calcium Phosphate.

8. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the disintegrants are selected but not limited to Sodium Starch Glycolate and/or Croscarmellose Sodium and/or crospovidone and/or starch and/or pregelatinised starch.

9. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the binders and film coating agents are selected but not limited to Hydroxypropylmethylcellulose and/or Polyvinylpyrrolidone and/or Hydroxypropylcellulose.

10. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the wetting agent is selected but not limited to sodium lauryl sulfate and/or tween 80.

11. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the solvents for suspending and/or dissolving Thiazolidinedione is selected but not limited to methanol and/or ethanol and/or dimethylformamide and/or dimethylsulfoxide and/or water and/or methylene chloride.

12. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1,2 and 9 wherein, the plasticizers are selected but not limited to tween 80 and/or triacetin and/or polyethylene Glycol.

13. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1,2 9 and 12 wherein, the plasticizers comprises of 5-25%by weight of the said polymer.

14. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the lubricants and glidants are selected but not limited to talc and/or colloidal silicon dioxide and/or Stearic acid and/or stearates of metal like calcium, magnesium and/or Glycerine monostearate.

15. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the Thiazolidinedione is released immediately form the second layer in-vitro.

16. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the second layer has upper surface & lower surface only one of those surface being in contact with the first layer.

17. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the second layer comprising of thiazolidinedione completely encloses / envelopes / covers / encircles the first layer containing biguanide.

18. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the tablet is enrobed into soft gelatin ribbons for ease of swallowing & / or for additional protection against photodegradation & oxidation & / or for taste masking and / or identification without altering the dissolution profile.

19. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein the first layer comprises of 50-80% by weight of Biguanide.

20. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, the second layer comprises of 5-50% by weight of thiazolidinedione.

21. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 wherein, Biguanides and Thiazolidinediones are used for controlling non-insulin dependent diabetes mellitus (Type II).

22. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 and 21 wherein the Biguanides is selected from the group consisting of Metformin, Buformin and Phenformin and their Pharmaceutical acceptable salts.

23. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1and 21 wherein, the Thiazolidinediones is selected from the group consisting of Pioglitazone, Rosiglitazone, Troglitazone and theirs Pharmaceutically acceptable salts there of.

24. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1, 21 and 22 wherein, the biguanide is Metformin HCl.

25. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1, 21 and 23 wherein, the Thiazolidinediones is selected from the group consisting of Pioglitazone HCl.

26. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1 and 25 wherein, Pioglitazone HCl has a particle size of minimum of 150 microns or less for improvisation of the bioavailability.

27. A process for manufacture of novel drug delivery multilayer tablet composition as claimed in claim 1, 24 and 25 wherein, the dose of Metformin HCl per tablet is in the range of 500mg -2000mg and the dose of Pioglitazone HCl equivalent to Pioglitazone per tablet is in the range of 15 - 60 mg and dosage regime is 1-4 tablets once a day.

Dated this 14th day of June, 2002

B.S.Shah

(Bharat S. Shah)

Duly constituted Attorney